

Efficacy of Bromocriptine to Reduce Body Temperature in
Febrile Critically-ill Adults With Acute Neurologic Disease: an
Open-label, Blinded Endpoint, Randomized Controlled Trial

NCT03496545

Document Date: 02/17/2021

Study Application (Version 1.12)

1.0 General Information		
*Enter the full title of your study:		
Efficacy of bromocriptine to reduce body temperature in febrile critically-ill adults with acute neurologic disease: an open-label, blinded endpoint, randomized controlled trial		
*Enter the study number or study alias		
Bromocriptine for Fever Trial or The BFF trial * This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.		

2.0 Add Department(s)						
2.1 List the departments associated with this study. The Principal Investigator's department should be Primary.:						
<table><tr><td>Primary Dept?</td><td>Department Name</td></tr><tr><td><input checked="" type="radio"/></td><td>UCSF - 140020 - M_Neurology</td></tr></table>	Primary Dept?	Department Name	<input checked="" type="radio"/>	UCSF - 140020 - M_Neurology		
Primary Dept?	Department Name					
<input checked="" type="radio"/>	UCSF - 140020 - M_Neurology					

3.0 List the key study personnel: (Note: external and affiliated collaborators who are not in the UCSF directory can be identified later in the Qualifications of Key Study Personnel section at the end of the form)		
3.1 *Please add a Principal Investigator for the study:		
<div>Kim, Anthony S</div> <div>Select if applicable</div> <div><input type="checkbox"/> Department Chair</div> <div><input type="checkbox"/> Resident</div> <div><input checked="" type="checkbox"/> Fellow</div> <div>If the Principal Investigator is a Fellow, the name of the Faculty Advisor must be supplied below.</div>		
3.2 If applicable, please select the Research Staff personnel:		
A) Additional Investigators		

Ch'ang, Judy Co-Principal Investigator Schell-Chaple, Hildegarde M Other Investigator		
B) Research Support Staff		
Chyall, Lawrence Study Recruiter Mcguire, Daniel W Study Recruiter Nguyen, Melissa N Study Recruiter Randazzo, Dominica B Study Coordinator Singhal, Neel MD, PHD, MD PHD Study Recruiter Slown, Kristin Study Recruiter Tran, Nhat Biostatistician Trillanes, Michael R Study Recruiter Villaroman, Andrea L Study Coordinator Vuong, Maximilian N Study Coordinator Winkelman, Amy Study Recruiter		
3.3 *Please add a Study Contact:		
Kim, Anthony S Randazzo, Dominica B The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).		
3.4 If applicable, please add a Faculty Advisor/Mentor:		
Kim, Anthony S		
3.5 If applicable, please select the Designated Department Approval(s):		

Josephson, Scott MD

Department Chair

Add the name of the individual authorized to approve and sign off on this protocol from your Department (e.g. the Department Chair or Dean).

4.0

Initial Screening Questions

Updated June 2017

4.1 * PROJECT SUMMARY: (REQUIRED) Give a brief overview of this project (250 words or less). Tell us what this study is about, who is being studied, and what it aims to achieve. If you have an NIH Abstract, paste it here: Click on the orange question mark to the right for more detailed instructions.

Up to 70% of patients with acute neurologic injury such as subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), traumatic brain injury (TBI), subdural hematomas (SDH) and ischemic stroke have fevers during their intensive care stay. Several studies have demonstrated that with acute neurologic injury, fever is associated with increased mortality, worse functional outcomes, and a longer ICU and hospital course. Thus, it has become standard of care to immediately and aggressively treat fever in this population. In addition to treating the etiology of fever, patients will receive continuous acetaminophen, ice packs, and external cooling to decrease their temperature. However, current antipyretic therapy is not effective and patients are subjected to the pain of physical cooling, sedatives, and anti-shivering medications. Acetaminophen only decreases the daily average temperature by 0.28°C and the peak effect is in the first two hours. Furthermore, external cooling devices for SAH are associated with increased frequency of tracheostomy, sedative use, and ICU length of stay. Thus, we must find a better way to establish normothermia.

Bromocriptine, a dopamine receptor agonist, acts at the hypothalamus. Already FDA approved in several diseases, bromocriptine is known for its antipyretic effect in neuroleptic malignant syndrome and paroxysmal sympathetic hyperactivity. In recent case reports, bromocriptine successfully treated refractory central fever. There is one published prospective study of giving bromocriptine to severe TBI patients to prevent central fever. Here, we propose to evaluate the acute antipyretic effects of bromocriptine in any etiology of fever in this critically-ill population. Despite its antipyretic activity in specific febrile syndromes, bromocriptine has never been prospectively studied as a more general antipyretic in the acute setting. If shown to be effective, this medication could prevent the detrimental outcomes associated with fever and improve antipyretic management in the ICU.

4.2 * HUD DEVICE: (REQUIRED) Does this application involve a [Humanitarian Use Device](#) (HUD):

- ☒ No
- ☐ Yes, and it includes a research component
- ☐ Yes, and it involves clinical care ONLY

4.3 * TYPE OF RESEARCH: (Click the Help link for definitions and guidance): (REQUIRED)

- ☒ Biomedical research
- ☐ Social, behavioral, educational, and/or public policy research

- ☐ Hybrid - includes aspects of BOTH types of research (check this option if your research is mainly social/behavioral but also involves specimen collection or blood draws to look at biological measures)

4.4 * SUBJECT CONTACT: (REQUIRED) Does this study involve ANY contact or interactions with participants:

- ☒ Yes (including phone, email or web contact)
☐ No (limited to medical records review, biological specimen analysis, and/or data analysis)

4.5 * RADIATION EXPOSURE: Does your protocol involve any radiation exposure to patients/subjects EITHER from standard care OR for research purposes (e.g., x-rays, CT-scans, DEXA, CT-guided biopsy, radiation therapy, or nuclear medicine including PET, MUGA or bone scans): (REQUIRED)

- ☐ Yes ☒ No

4.6 * RISK LEVEL: (REQUIRED) What is your estimation of the risk level, including all screening procedures and study activities (Help Text updated 9/13):

- ☐ Minimal risk
☒ Greater than minimal risk

4.7 * REVIEW LEVEL: (REQUIRED) Requested review level (Click on the orange question mark to the right for definitions and guidance):

- ☒ Full Committee
☐ Expedited
☐ Exempt

4.11 * CLINICAL TRIAL: (REQUIRED) Is this a clinical trial? According to The World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) a clinical trial is:

- Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

ICMJE requires registration of a clinical trial in a public database (such as ClinicalTrials.gov) prior to enrollment, for eventual publication of results in member biomedical journals.

Guidance: Public Law 110-85 requires that all investigators who perform an *applicable clinical trial* must ensure that the trial is registered on a government web site called ClinicalTrials.gov. The FDA requires registration for "applicable clinical trials," defined as follows:

- For any trials of drugs and biologics: controlled clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation.
- For trials of biomedical devices: controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and pediatric post-market surveillance.

For additional information on the ClinicalTrials.gov registration process at UCSF and the definition of a clinical trial for purposes of registration, visit the ClinicalTrials.gov section of the UCSF Clinical Research Resource HUB.

☒ Yes ☐ No

Clinical Trial Registration

"NCT" number for this trial:

NCT03496545

If you don't yet have the NCT#, type 'Pending.'

4.12 * CLINICAL TRIAL PHASE (REQUIRED) Check the applicable phase(s) (Help Text updated 9/13):

- ☐ Phase I
☒ Phase II
☐ Phase III
☐ Phase IV

4.13 * INVESTIGATOR-INITIATED: (REQUIRED) Is this an investigator-initiated study:

☒ Yes ☐ No

4.14 * CANCER: (REQUIRED) Does this study involve cancer (e.g., the study involves patients with cancer or at risk for cancer, including behavioral research, epidemiological research, public policy research, specimen analysis, and chart reviews):

☐ Yes ☒ No

If you don't know if you should answer 'Yes' or 'No,' please [email](#) the Cancer Center's Protocol Review Committee for help.

4.15 SCIENTIFIC REVIEW: If this study has undergone scientific or scholarly review, please indicate which entity performed the review (check all that apply):

- ☐ Cancer Center Protocol Review Committee (PRC) (Full approval is required prior to final CHR approval for cancer-related protocols.)
☐ CTSI Clinical Research Services (CRS) Advisory Committee
☐ CTSI Consultation Services
☐ Departmental scientific review
☐ Other:

4.16 * STEM CELLS: (REQUIRED) Does this study involve [human stem cells](#) (including iPS cells and adult stem cells), gametes or embryos:

- ☒ No
☐ Yes, and requires IRB and GESCR review
☐ Yes, and requires GESCR review, but NOT IRB review

4.17 * **FINANCIAL INTERESTS: (REQUIRED)** Do you or any other responsible personnel (or the spouse, registered domestic partner and/or dependent children thereof) have financial interests related to this study:

☐ Yes ☒ No

5.0 Funding

5.1 * **FEDERAL FUNDING: (REQUIRED)** Is this study currently supported in whole or in part by Federal funding, even by a subcontract, OR has it received ANY Federal funding in the past:

☐ Yes ☒ No

5.2 * **DoD INVOLVEMENT:** Is this project linked in any way to the Department of Defense (DoD): (REQUIRED)

☐ Yes ☒ No

5.3 **SPONSORS:** Identify all sponsors and provide the funding details. If funding comes from a Subcontract, please list only the Prime Sponsor:

External Sponsors:

View Details	Sponsor Name	Sponsor Type	Awardee Institution	Contract Type:	UCSF RAS "P number" or eProposal number	UCSF RAS System Award Number ("A" + 6 digits)

No Sponsor has been added to this IRB Study

If the funding is coming through UCSF and you don't know the A or P number, you can search the eProposal side for the contract or grant (this does NOT replace adding the sponsor by name above AND entering the A or P number):

Project Status	Proposal Number	Project Title	Principal Investigator
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No Projects are Linked to this IRB Study

Other Funding Sources and Unfunded Research - Gift, Program, or Internal Funding (check all that apply):

<div><div><input type="checkbox"/> Funded by gift (specify source below)</div><div><input type="checkbox"/> Funded by UCSF or UC-wide program (specify source below)</div><div><input type="checkbox"/> Specific departmental funding (specify source below)</div><div><input checked="" type="checkbox"/> Unfunded (miscellaneous departmental funding)</div><div><input type="checkbox"/> Unfunded student project</div></div>	
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6.0 Sites, Programs, Resources, and External IRB Review

6.1 UCSF AND AFFILIATED SITES (check all that apply):

☐ UCSF (including Laurel Heights and all the other sites outside the main hospitals)

☒ Parnassus

☐ Mission Bay

☐ China Basin

☐ Mount Zion

☐ Helen Diller Family Comprehensive Cancer Center

☐ Langley Porter Psychiatric Institute

☒ San Francisco General Hospital (SFGH)

☐ SF VA Medical Center (SF VAMC)

☐ Blood Centers of the Pacific (BCP)

☐ Blood Systems Research Institute (BSRI)

☐ Fresno Community Medical Center

☐ Gallo

☐ Gladstone

☐ Jewish Home

☐ Institute on Aging (IOA)

☐ SF Dept of Public Health (DPH)

Research involving SFGH: You are required to obtain additional approvals from the SFGH Dean's Office. Download the SFGH Protocol Application Form and submit the completed form to the SFGH Dean's Office.

6.2 LOCATIONS: At what locations will study visits and activities occur:

UCSF Parnassus - Neuro ICU 8 and Neuro ICU 11

Zuckerberg San Francisco General Hospital - Neuro ICU

6.3 OFF-SITE PROCEDURES: Will any study procedures or tests be conducted off-site by non-UCSF personnel:

☐ Yes

☒ No

6.4 RESEARCH PROGRAMS: Check any UCSF research programs this study is associated with:	
<div><input type="checkbox"/> Cancer Center</div> <div><input type="checkbox"/> Center for AIDS Prevention Sciences (CAPS)</div> <div><input type="checkbox"/> Global Health Sciences</div> <div><input type="checkbox"/> Immune Tolerance Network (ITN)</div> <div><input type="checkbox"/> Neurosciences Clinical Research Unit (NCRU)</div> <div><input type="checkbox"/> Osher Center</div> <div><input type="checkbox"/> Positive Health Program</div>	
6.5 * CTSI CRS SERVICES: (REQUIRED) Will this study be carried out at one of the UCSF Clinical Research Services (CRS) units or utilize CRS services :	
<div><input type="radio"/> Yes <input checked="" type="radio"/> No</div>	
6.6 * MULTI-CENTER TRIAL: (REQUIRED) Is this a multicenter research trial? By multi-center trial, we mean a study where the protocol is developed by an industry sponsor, consortium, a disease-group, etc., who then selects sites across the nation or in different countries to participate in the trial. The local sites do not have any control over the design of the protocol.	
<div><input type="radio"/> Yes <input checked="" type="radio"/> No</div>	
6.7 OTHER SITE TYPES: Check all the other types of sites not affiliated with UCSF with which you are cooperating or collaborating on this project: Do NOT check any boxes below if this is a multi-center clinical trial, UCSF is just one of the sites, and neither UCSF nor its affiliates are the coordinating center.	
<div><input type="checkbox"/> Other UC Campus</div> <div><input checked="" type="checkbox"/> Other institution</div> <div><input type="checkbox"/> Other community-based site</div> <div><input type="checkbox"/> Foreign Country</div> <div><input type="checkbox"/> Sovereign Native American nation (e.g. Navajo Nation, Oglala Sioux Tribe, Havasupai, etc.)</div>	
6.10 * RELYING ON AN EXTERNAL IRB: Does this application include a request to rely on an external IRB other than the NCI IRB (e.g. UC reliance, private/commercial IRB, or institutional IRB): (REQUIRED) Check out the orange question mark to the right to find out if your study is eligible for external IRB review.	
<div><input type="radio"/> Yes <input checked="" type="radio"/> No</div>	

7.0 Outside Site Information

7.1 Outside Site Information

Click "Add a new row" to enter information for a site. Click it again to add a second site again to add a third site, a fourth site, etc.

 [Click here to view this form.](#)

Outside Site Information	
Non-UCSF affiliated site information:	
Site name: Weill Cornell	
Contact name: Judy Ch'ang	
Email: jhc9010@med.cornell.edu	
Phone: 419-324-5828	
For Federally-funded studies only, corresponding FWA#:	
NA	
* The research at this site will be reviewed by:	
<div><div><input type="radio"/> The non-affiliated site's IRB or a private IRB</div><div><input type="radio"/> The non-affiliated site is requesting UCSF to be the IRB of record for this study</div><div><input checked="" type="radio"/> The non-affiliated site is not engaged in the human subjects research and has provided a letter of support</div></div> <p>If the other site's IRB approval letter is available now, attach it to the application. If the IRB approval letter is not yet available, submit it once you receive it.</p> <p>Or, if the other site is not engaged in human subjects research, attach the letter of support to your application.</p>	

8.0 Research Plan and Procedures

8.1 This new consolidated section requests information about:

- Hypothesis
- Aims
- Study Design
- Background and Significance
- Preliminary Studies
- Procedures
- Statistical Methods
- References

Later sections include:

- Drugs and Devices
- Sample Size, Eligibility, and Subjects
- Recruitment and Consent
- Risks and Benefits
- Data and Safety Monitoring Plan
- Confidentiality, Privacy and Security
- Financial Considerations
- Qualifications of Personnel
- Other Approval and Registrations

8.2 HYPOTHESIS: Describe the hypothesis or what the study hopes to prove (Help Text updated 9/13):

There is a significant reduction in body temperature over 48 hours after administration of bromocriptine and acetaminophen compared to acetaminophen alone in febrile critically ill patients in the neuro intensive care unit.

8.3 AIMS: List the specific aims:

Aim 1. To evaluate the effect of bromocriptine in addition to standard acetaminophen therapy compared to acetaminophen alone on total body temperature burden above 37°C over 48 hours when administered within 1 hour of fever >38.3°C in patients with subarachnoid hemorrhage, intracerebral hemorrhage, traumatic brain injury, subdural hematomas and ischemic stroke in the neurologic intensive care unit.

Aim 2. To evaluate the safety of bromocriptine in febrile patients with subarachnoid hemorrhage, intracerebral hemorrhage, traumatic brain injury, subdural hematomas and ischemic stroke in the neurocritical care intensive care unit.

8.4 DESIGN: Briefly describe the study design (e.g., observational, interventional, randomized, placebo-controlled, blinded, cross-over, cross-sectional, longitudinal, pharmacokinetic, etc.):

Two-center, open-label, blinded end-point, interventional, randomized, controlled trial.

8.5 BACKGROUND AND SIGNIFICANCE: Briefly provide the background and significance of this study (e.g. why is this study needed) (space limit: one half page):

If this is a first in humans study, please summarize the safety data from the animal studies. For pediatric drug or device studies, please identify if this is the first study in pediatric populations.

Up to 70% of patients with acute neurologic injury have fevers during their intensive care hospital course. Preclinical animal models demonstrate that hyperthermia, through various mechanisms, causes worsening brain injury. In human studies, fever is an independent predictor of poor outcome including increased mortality rates, longer hospital stays, depressed level of consciousness, and worse functional outcomes. **Thus, it has become standard of care to aggressively control fever in this population but current antipyretic therapy is not very effective and external cooling subjects patients to the pain of physical cooling, sedatives, and other medications to prevent shivering.** Acetaminophen decreases the daily average temperature by only ~0.28°C and its peak effect is within the first two hours then quickly declines. Furthermore, external cooling devices for SAH are associated with increased sedative use, longer ICU stays, and a higher frequency of tracheostomy. Bromocriptine is a dopamine D2 receptor agonist which acts at the hypothalamus. Since it is already FDA-approved for several other indications, there is extensive clinical experience on its safety and tolerability with maximum dosing of 100mg/day. Its potential use as a more general antipyretic for all etiologies of fever is suggested by the clear antipyretic effect seen in neuroleptic malignant syndrome (NMS), paroxysmal sympathetic hyperactivity (PSH) and several case reports which demonstrate bromocriptine’s effectiveness in treating refractory central fever. In a prospective study evaluating bromocriptine’s acute antipyretic effect in 50 severe TBI patients, the findings suggested that early administration of bromocriptine could safely prevent center fever.

The dosing for this proposed study, bromocriptine 5mg every 4 hours (30mg daily total), is modified off of the dosing recommendations for NMS, PSH, and the aforementioned study in TBI. Examining the literature regarding the dosing for NMS, various doses were trialed and uptitrated to effect. There were various starting doses from 2mg every 12 hours to 5mg every 4 hours uptitrated to 15mg every 8 hours. The purpose of starting at a higher dose of 5mg every 4 hours is to establish efficacy of the antipyretic effect given that there is currently no established dosing for this indication.

While dizziness, fatigue, headache, constipation, nausea, skeletal muscle weakness, rhinitis, orthostatic hypotension and sleepiness have been reported across different dosages and disease states from clinical trials, all of these studies in critically-ill patients reported no serious adverse events. In Parkinson's Disease patients, there seemed to be a cumulative dosing effect on increasing the risk of valvular heart disease. In a retrospective study evaluating 72 bromocriptine patients and 47 control, the mean cumulative dose was 20053.7mg +/-17660.9 mg and patients were treated for a mean duration of 43 months. The patients in this study will only be exposed to 30mg daily for 48 hours. Given that the pathogenesis of both infectious and noninfectious fever revolves around the hypothalamus, and we have evidence that bromocriptine has an antipyretic effect at the hypothalamus, we deduce that bromocriptine could be used more broadly to treat all fevers in the acute setting and not just refractory central fevers. Here, we propose to evaluate the acute antipyretic effects of bromocriptine in this critically-ill population through a **pilot, open label, blinded endpoint, randomized controlled trial**. It is imperative that in this population already stricken with significant mortality and morbidity, we develop better methods of achieving normothermia to prevent the detrimental outcomes that fever has on the already injured brain. **Data from this pilot study would form the basis for a definitive study on the impact of bromocriptine on outcomes in neuro ICU patients.**

8.6 PRELIMINARY STUDIES: Briefly summarize any preliminary studies relevant to your proposed research (space limit: one half page):

Although there are several case reports, a retrospective study in SAH, and a prospective RCT in TBI, significant limitations exist and many questions regarding the use of bromocriptine still remain. These case reports describe patients with mostly ICH and one with mixed autonomic hyperactivity disorder who all underwent extensive infectious and noninfectious work ups. Patients were treated with current antipyretic management; but, they were only responsive to bromocriptine, suggesting an antipyretic effect in refractory fevers in acute neurologic illnesses. However, bromocriptine was not administered immediately upon fever diagnosis and not all of the specific dosing regimens were reported. Then in 2017, an Egyptian group published a prospective randomized control trial (N=50) in severe TBI patients where bromocriptine was administered upon admission. This trial did not state the duration of treatment, nor did they define what medications/interventions were in the control therapy group. They demonstrated that bromocriptine could be safely administered in the acute setting of TBI. Recently, an abstract was published which retrospectively evaluated eight aneurysmal subarachnoid hemorrhage patients who received bromocriptine and found no significant difference in median time to fever cessation and length of ICU or hospital stay. The abstract does not provide how the comparison group was chosen, the dosing of bromocriptine, the difference of antibiotic use, and if all patients were exposed to the same cooling practices amongst many other confounding factors. They do admit that prospective studies are warranted. With all of this initial data on bromocriptine's antipyretic effect, still no study exists which prospectively evaluates this drug's efficacy in the acute setting for all etiologies of fever in a heterogeneous population of acute neurologic illness. These cases and studies have suggested bromocriptine's efficacy and safety in refractory fevers and in the acute setting. However, we need a prospective randomized trial which evaluates a standard antipyretic dosing of bromocriptine and its use not as fever prophylaxis but as immediate fever treatment in SAH, TBI, ICH, SDH and ischemic stroke. Prior data hints at bromocriptine's potential to change antipyretic management and this study is protocolled and powered to investigate just that.

8.7 * TREATMENT PROTOCOL: Is this a treatment study, i.e. does this study intend to provide treatment to individuals with a medical or psychological condition: (REQUIRED)

☒ Yes ☐ No

8.8 * BILLABLE PROCEDURES: Does this study involve any services or procedures (e.g. physical exams, surgeries, lab tests, imaging studies, or drugs) that could be billable to patients, their insurance, Sponsor, or any other entity (answer 'Yes' even if the study is going to pay for all the procedures): (REQUIRED)

☒ Yes ☐ No

If you are not sure if your study involves billable procedures, send an email to the **UCSF Office of Clinical Research (OCR)** for help answering this question.

8.9 * COMMON RESEARCH ACTIVITIES: Types of research activities that will be carried out. Check all that apply and describe in more detail in the 'Procedures / Methods' section: (REQUIRED)

- ☒ Interviews, questionnaires, surveys
- ☐ Educational or cognitive tests
- ☐ Focus groups
- ☐ Observation
- ☐ Non-invasive imaging or testing (MRI, EEG, pulse oximetry, etc.)
- ☐ Administration of contrast agent
- ☐ Imaging procedures or treatment procedures that involve radiation (x-rays, CT scans, CT-guided biopsies, DEXA scans, MUGA or PET scan)

- ☐ Biopsy conducted solely for research purposes
- ☐ Use of placebo
- ☐ Sham surgical procedure
- ☐ Collection of data from wearable tech such as Fitbit, Apple Watch, Garmin, motion actigraphs, etc.)
- ☐ Fitness tests or other exertion activities
- ☐ Use of mobile health apps or other apps
- ☐ Social media-based research activities
- ☐ None of the above

8.10 * PROCEDURES / METHODS: (REQUIRED)

For clinical research, list all study procedures, tests and treatments required for this study, including when and how often they will be performed. If there are no clinical procedures, describe the research activities.

If some of the activities would occur even if the person were not in the study, as in the case of treatment or tests performed for diagnostic purposes, clearly differentiate between those activities that will be done solely for research purposes and those that are happening as part of routine care.

Examples may include:

- additional scans outside standard clinical diagnosis or monitoring
- additional biopsies to collect tissue for research
- extra clinic visits
- extra lab tests not required for clinical care

If you have a procedure table, attach it to the submission with your other study documents.

1. Communicate with primary team physician about patient's eligibility to participate in study.
2. Screen and consent all patients/surrogates upon arrival to the ICU: signed consent in patient chart. Copy to send to pharmacy.
3. Screen body temperature from routine thermometry methods used in ICUs for temperatures $\geq 38.3^{\circ}\text{C}$ for routine care through esophageal, bladder, or rectal means. Patients at SFGH must be attached to a Moberg monitor. All apart of routine care.
4. Enroll patient when body temperature $\geq 38.3^{\circ}\text{C}$: Activate study protocol.
5. If for any reason, the patient or surrogate decides they initially do not want to participate in the study but then later would like to participate after the patient becomes febrile, the research team will re-screen the patient to make sure the patient is still eligible. If the patient is eligible, they can be enrolled; medical intervention administration will be based off of 1) the washout period of any antipyretics given prior to enrollment and 2) body temperature of the patient $\geq 38.3^{\circ}\text{C}$ within 1 hour of study drug administration.

6. Preprinted provider order for study drug

1. Provider signature (Critical Care Medicine Physician or Primary team)
2. Order in chart and copy sent to pharmacy with copy of signed consent.
3. Pharmacy to randomize and prepare blinded study drug within 30 minutes.

7. Intervention: bromocriptine 5mg every 4 hours PO/NG/FT and acetaminophen 650mg every 4 hours PO/NG/FT for 48 hours, initiated within 1 hour after temperature reading $\geq 38.3^{\circ}\text{C}$. Control: acetaminophen 650mg every 4 hours PO/NG/FT for 48 hours, initiated within 1 hour after temperature reading $\geq 38.3^{\circ}\text{C}$.

8. Measure temperature every 3 seconds from initial drug administration if patient has a rectal, esophageal, or urinary temperature probe. These probes used are in routine care. The patient must maintain one of these temperature probes for the 48 hour duration of study.

9. During each nursing shift starting from first medication administration during the 48 hour study period, the bedside nurse will do a 5-minute assessment, thus a total of 4 assessments.

10. At the end of every shift from first medication administration for the next 48 hours, please complete this 5-minute assessment:

1. During your shift, has the patient had episodes of decreases in systolic pressures $>20\text{mm Hg}$ or diastolic pressures $>10\text{mm Hg}$ respectively? If no, please go to question 2. [yes] [no]

1a. If you answered yes, how many episodes of decreases in systolic pressures $>20\text{mm Hg}$ or diastolic pressures $>10\text{mm Hg}$ respectively occurred? ____

1b. How many episodes of systolic blood pressure $< 90\text{mm Hg}$ occurred? ____

1c. Were any of these episodes associated with dizziness or lightheadedness? [yes] [no] [not applicable/patient cannot answer]

1d. Were these episodes associated with position change or movement? ____

1f. How many episodes received treatment? ____

1g. Were these episodes within the first 2 hours of receiving the first dose of bromocriptine? (Only answer if you started bromocriptine on your shift) [yes] [no]

2. During your shift, has the patient had headache? [yes] [no] [patient not able to report]

If no or patient not able to report, please go to question 3.

2a. Were the headaches (circle all that apply) [mild] [moderate] [severe]

2b. How many headaches received an intervention? ____

2c. How many headaches self-resolved? ____

2d. Were these headaches within the first 2 hours of receiving the first dose of bromocriptine? (Only answer if you started bromocriptine on your shift) [yes] [no]

3. In the last 12 hours, has the patient experienced nausea? [yes] [no] [patient not able to report] If no or patient

3a. How many episodes of nausea self-resolved? ____

3b. How many episodes of nausea received an intervention? ____

3c. Were these episodes of nausea within the first 2 hours of receiving the first dose of bromocriptine? (Only answer if you started bromocriptine on your shift) [yes] [no]

11. No physical cooling (fans, ice packs, cooling blanket) during study period.

12. No administration of other antipyretics (medications containing acetaminophen, NSAIDs and Aspirin > 300 mg) during study period.

13. Rescue protocol: If temperature increases to > 40°C during 48 hour study period, the primary team provider will be notified. Physical cooling or antipyretic medication interventions may be ordered at the discretion of the provider. All body temperature altering interventions will be recorded.

14. If heart rate or blood pressure increase or decrease beyond ordered notification parameters, the nurse will contact the primary team provider per routine standard of care.

15. After the trial period is over, other clinical data will be extracted from the chart retrospectively such as laboratory and culture data, antibiotic use, and days spent in ICU. Please see protocol attachment, schedule of activities.

16. 30 Day Follow-up

Subjects or surrogates, family members, friends, medical health professionals taking care of the patient will be contacted by phone at 30 days to complete a modified rankin score. They will be given the 30 day phone call form which lists the questions they will be asked. This assessment will be completed by a study team member and will take approximately 15 minutes. The phone script: Hello, my name is xxxx and I am calling from UCSF Medical Center or Zuckerberg San Francisco General Hospital. This is a follow up call for [participant name]. Is it possible for me to speak to that person or [surrogate, family, friend, medical health professional taking care of the patient]? Great. Were you or [patient name] admitted to [UCSF or ZSFGH] for [SAH, TBI, ICH, or ischemic stroke]? I am calling about the fever study, bromocriptine for fever, that [you or patient name] took part of. Is this a convenient time to talk for about 15 minutes or arrange a time that is better?"

If the patient remains in an institutional setting at 30 days and is unable to speak on the phone, then the medical health professionals caring for the patient may be able to answer the questions regarding their functional status as stated in the new consent form. If the patient is in a home setting but is unable to speak on the phone for any reason, then family, friend or caretaker may also answer questions about their functionality which is stated in the new consent form. Non-English speakers will be interviewed using the hospital certified language interpreters which can call in on the phone and interpret the conversation.

The 30 day phone call document states that

"A member of the research team will be contacting you or your legally authorized representative, surrogate, friend, family member, or medical health care professional taking care of you in 30 days to see how you are doing. This phone call will only take approximately 15 minutes and will ask the following questions to assess how you are doing." Then the document lists the questions being asked.

1. Do you have any symptoms that are bothering you? yes ___ no ___

2. Are you able to do the same work as before? yes ___ no ___

3. Are you able to keep up with your hobbies? yes ___ no ___

4. Have you maintained your ties to friends and family? yes ___ no ___

5. Do you need help making a simple meal, doing household chores, or balancing a checkbook? yes

- ___

no

6. Do you need help with shopping or traveling close to home? yes ___ no ___
7. Do you need another person to help you walk? yes ___ no ___
8. Do you need help with eating, going to the toilet, or bathing? yes ___ no ___
9. Do you stay in bed most of the day and need constant nursing care? yes ___ no ___

From these answers, the research team member will then use an online modified rankin calculator to calculate the mRS. mRS calculator website at: <http://www.modifiedrankin.com/> and click on the blue box **"Continue to the Data Entry Page."** Enter patient/proxy answers. Click on the blue box **"Calculate the mRS"**.

For the patients previously enrolled and still admitted in the hospital whose surrogates signed the consent form without the new modification regarding the 30 day phone follow up, I will re-consent them with the new consent form and submit to APEX in order to reach them in 30 days.

8.11 STANDARD CLINICAL PRACTICE: To what extent, if any, do the planned research procedures differ from the care that people would otherwise receive at this institution or the study site if not being done locally:

Currently standard clinical practice at UCSF Parnassus is giving acetaminophen but dosing and frequency vary per treating team. Then the use of external cooling blankets or intravascular cooling device is also variable and depends on the treating team or even bedside nurse.

At the beginning of this year, Zuckerberg San Francisco General Hospital adopted a Fever Management protocol for Critical Neurological Injury, TBI, and Stroke. To achieve a goal temperature of 37.5°C, the following will be done: continuous core temperature monitoring with esophageal probe and rectal or bladder probe. Document temperature q 1 hour and PRN. Acetaminophen will be initiated: 650 mg PO/FT q 4 hours ATC. Give PR if unable to give PO/FT. NTE 4 gm in 24 hrs. Discontinue any prior acetaminophen orders. Obtain blood cultures x2, urine and tracheal aspirate cultures q 48 hours. For temperature >38.3°C sustained for 2 or more hours: Initiate surface cooling per Critical Care Department Policy No. 31.0 "Zoll InnerCool STx—External Temperature System". Call MD for drop in temperature of more than 1°C every 15 minutes. Then, for fever not adequately managed by surface cooling within 8 hours the primary service will consult Neurocritical Care for intravascular cooling catheter placement.

In this study, if a patient has a temperature ≥ 38.3°C, the patients will be randomized to the control or intervention arm. Control is currently standard of care as the use of surface cooling is based on provider preference. No other methods for physical cooling (fans, ice packs, cooling blanket, external/intravascular cooling) or other antipyretics such as NSAIDS or aspirin >300mg will be permitted during the 48-hour study period unless the temperature increases to > 40°C during the study period or unless required for standard clinical care (e.g. for ischemic stroke patients).

8.12 INSTRUMENTS: List all questionnaires, surveys, interview, or focus group guides that will be used for this study:

At the end of every shift from first medication administration for the next 48 hours, please complete this 5-minute assessment:

1. During your shift, has the patient had episodes of decreases in systolic pressures >20mm Hg or diastolic pressures >10mm Hg respectively? If no, please go to question 2. [yes] [no]

1a. If you answered yes, how many episodes of decreases in systolic pressures >20mm Hg or diastolic pressures >10mm Hg respectively occurred? ____

1b. How many episodes of systolic blood pressure < 90mm Hg occurred? ____

1c. Were any of these episodes associated with dizziness or lightheadedness? [yes] [no]
[not applicable/patient cannot answer]

1d. Were these episodes associated with position change or movement? ____

1f. How many episodes received treatment? ____

1g. Were these episodes within the first 2 hours of receiving the first dose of bromocriptine?
(Only answer if you started bromocriptine on your shift) [yes] [no]

2. During your shift, has the patient had headache? [yes] [no] [patient not able to report]

If no or patient not able to report, please go to question 3.

2a. Were the headaches (circle all that apply) [mild] [moderate] [severe]

2b. How many headaches received an intervention? ____

2c. How many headaches self-resolved? ____

2d. Were these headaches within the first 2 hours of receiving the first dose of bromocriptine?
(Only answer if you started bromocriptine on your shift) [yes] [no]

3. In the last 12 hours, has the patient experienced nausea? [yes] [no] [patient not able to report] If no or patient

3a. How many episodes of nausea self-resolved? ____

3b. How many episodes of nausea received an intervention? ____

3c. Were these episodes of nausea within the first 2 hours of receiving the first dose of bromocriptine? (Only answer if you started bromocriptine on your shift) [yes] [no]

30 Day Phone call FU: Modified Rankin Score (MRS assessment)

The 30 day phone call document states that

"A member of the research team will be contacting you or your legally authorized representative, surrogate, friend, family member, or medical health care professional taking care of you in 30 days to see how you are doing. This phone call will only take approximately 15 minutes and will ask the following questions to assess how you are doing." Then the document lists the questions being asked.

1. Do you have any symptoms that are bothering you? yes ___ no ___
2. Are you able to do the same work as before? yes ___ no ___
3. Are you able to keep up with your hobbies? yes ___ no ___
4. Have you maintained your ties to friends and family? yes ___ no ___
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook? yes ___ no ___
6. Do you need help with shopping or traveling close to home? yes ___ no ___
7. Do you need another person to help you walk? yes ___ no ___
8. Do you need help with eating, going to the toilet, or bathing? yes ___ no ___
9. Do you stay in bed most of the day and need constant nursing care? yes ___ no ___

From these answers, the research team member will then use an online modified rankin calculator to calculate the MRS.

Attach any unpublished instruments in the 'Other Study Documents' section of the Initial Review Submission Packet form after completing the study application. Published instruments should NOT be attached.

8.13 * BIOSPECIMEN COLLECTION: Are you drawing any blood or collecting other biosamples (e.g. tissue, buccal swabs, urine, saliva, hair, etc.): (REQUIRED)

☐ Yes ☒ No

8.26 STATISTICAL METHODS: Briefly summarize the methods and types of analyses that will be performed:

Using data from a prior published study of acetaminophen versus ibuprofen to estimate the standard deviation of the potential treatment effect, which assumes a standard deviation of 0.5°C, with 20 patients per group, we will have 80% power to detect a 0.46 °C group difference with a two-tailed α of 0.05. Based on the volume of neuroICU admissions and a prior study evaluating intravenous acetaminophen that enrolled 2-5 patients a month from just the UCSF Parnassus neuro ICU, we expect to be able to randomize 40 patients over an 8-month enrollment period at two institutions.

The primary endpoint of this study is the difference in total temperature burden $> 37^{\circ}\text{C}$ over 48 hours as captured by the area under the temperature—time curve (AUC) between the control and the intervention groups. We will calculate the AUC for each patient, derive the mean AUC in each group, and then compare these means using a paired t-test. We will use Fisher's exact test to compare the side effect profile between the two groups.

8.27 REFERENCES: List only the 5-10 most relevant references (a separate bibliography can be attached for reference purposes if this study involves novel approaches, agents, or an emerging technology that the IRB may not be familiar with):

1. Greer, D.M., et al., *Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis*. Stroke, 2008. 39(11): p. 3029-35.
2. Badjatia, N., et al., *Impact of induced normothermia on outcome after subarachnoid hemorrhage: a*

case-control study. *Neurosurgery*, 2010. 66(4): p. 696-700; discussion 700-1.

3. Kang, S.H., et al., *Bromocriptine for control of hyperthermia in a patient with mixed autonomic hyperactivity after neurosurgery: a case report*. *J Korean Med Sci*, 2012. 27(8): p. 965-8.

4. Natteru, P., et al., *Central Hyperthermia Treated with Bromocriptine*. *Case Rep Neurol Med*, 2017. 2017: p. 1712083.

5. Samudra, N. and S. Figueroa, *Intractable Central Hyperthermia in the Setting of Brainstem Hemorrhage*. *Ther Hypothermia Temp Manag*, 2016. 6(2): p. 98-101.

6. Yu, K.W., et al., *Effectively managing intractable central hyperthermia in a stroke patient by bromocriptine: a case report*. *Neuropsychiatr Dis Treat*, 2013. 9: p. 605-8.

7. Zakhary, T.S., Ahmed, *Bromocriptine in Central Hyperthermia after Severe Traumatic Brain Injury*. *Open Journal of Emergency Medicine*, 2017. 5: p. 102-109.

8. Reeder, J.C., RS.; Mittal, Manoj, *Time to Central Fever Cessation in Aneurysmal Subarachnoid Hemorrhage Patients with Bromocriptine - Abstract Only*. *Crit Care Med*, 2018. 46(1): p. 376.

9. Mullins, M.E., et al., *A prospective randomized study to evaluate the antipyretic effect of the combination of acetaminophen and ibuprofen in neurological ICU patients*. *Neurocrit Care*, 2011. 15(3): p. 375-8.

10. Tan LC, et al., *Bromocriptine use and the risk of valvular heart disease*. *Mov Disord*. 2009;24(3):344-9.

11. Rosenberg, M. R., & Green, M. (1989). Neuroleptic malignant syndrome. Review of response to therapy. *Arch Intern Med*, 149(9), 1927-1931.

9.0 Drugs and Devices

9.1 * DRUGS AND/OR BIOLOGICS: Are you **STUDYING** any drugs and/or biologics that are either approved or unapproved: **(REQUIRED)**

☒ Yes ☐ No

9.2 LIST THE DRUGS OR BIOLOGICS: List the drugs or biologics that will be studied. In the drug details screen you will be asked questions such as:

- Whether the drug or biologic is FDA approved
- If the drug or biologic will be provided at no cost
- If an IND is necessary, the IND number, and who holds the IND
- If the drug or biologic is FDA approved and an IND is not required, the rationale for the decision
- If the **Investigational Drug Service (IDS)** is dispensing the drug or biologic (required unless a **waiver** is obtained from the IDS)

Please see the **UCSF IRB website** for more details about the use of drugs and biologics in research, including the **IND Decision Worksheet**. Verification of IND numbers: If the sponsor’s protocol does not list the IND number, you must submit documentation from the sponsor or FDA identifying the IND number for this study. Attach this documentation in the Other Study Documents section of the Initial Review Submission Packet. **If you have any correspondence from the FDA or sponsor regarding this drug or biologic, please attach it to the application.**

View Details

Drug Name

FDA Approved

A new drug or a new use of approved drug:

IND Number

Trade Drug Name:

BROMOCRIPTINE MESYLATE

Generic Drug Name:

BROMOCRIPTINE MESYLATE

Yes

Yes

Investigational Drug Name:

Trade Drug Name:	BROMOCRIPTINE MESYLATE
Generic Drug Name:	BROMOCRIPTINE MESYLATE
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Mylan
Is the drug supplied at no cost?	No
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	Yes
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	An investigator proposes a small pilot study of an approved drug for a novel use and states that an IND is not needed because the data will not be submitted to the FDA. The investigator explains that if the pilot data looks promising a larger trial will be submitted with an IND. The IRB is likely to approve the pilot study without an IND because a small pilot study is an appropriate first step in determining whether a change in labeling should be sought.
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Will the investigational pharmacy be dispensing?	Yes
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	

Trade Drug Name:

ACETAMINOPHEN

Generic Drug Name:

ACETAMINOPHEN

Yes

No

Investigational Drug Name:

Trade Drug Name:	ACETAMINOPHEN
Generic Drug Name:	ACETAMINOPHEN
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	generic manufacturer from the investigational pharmacy
Is the drug supplied at no cost?	Yes
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	No
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	We are using the drug for its approved indication and it is standard of care.
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Will the investigational pharmacy be dispensing?	Yes
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	

9.3 * MEDICAL DEVICES: Are you **STUDYING** any medical devices, in vitro diagnostics, or assays that are either approved or unapproved:(**REQUIRED**)

☐ Yes ☒ No

9.6 * Is this an expanded access or compassionate use protocol, meaning the primary purpose is to diagnose, monitor or treat a patient's condition, rather than the collection of safety and efficacy data of the experimental agent: (**REQUIRED**)

☐ Yes ☒ No

10.0 Sample Size and Eligibility Criteria

10.1 ENROLLMENT TARGET: How many people will you enroll:

90

If there are multiple participant groups, indicate how many people will be in each group:

acetaminophen 650mg every 4 hours: N = 45

acetaminophen 650mg every 4 hours and bromocriptine 5mg every 4 hours: N = 45

A targeted enrollment of 30 subjects per group is planned to account for any patients who are discontinued or excluded due to the potential risk of instability and unplanned procedures related to their critical illness.

10.3 SAMPLE SIZE JUSTIFICATION: Explain how and why the number of people was chosen. For multi-site studies, this is referring to the number that will be enrolled across all sites:

Using data from a prior published study of acetaminophen versus ibuprofen to estimate the standard deviation of the potential treatment effect, which assumes a standard deviation of 0.5°C, with 20 patients per group (control arm n = 20, intervention arm n = 20), we will have 80% power to detect a 0.46 °C group difference with a two-tailed α of 0.05. A targeted enrollment has been increased to 90 because out of the 25 patients enrolled, 3 have been nonfebrile, 2 have received cooling blankets, 2 had missed doses because were away at procedures, 1 died secondary to withdrawal of care, 1 was withdrawn from the study (patient was doing well and family did not want to give him more medications). Thus out of enrolling 25 patients, 9 were not able to reach full analysis. Likely with every 25 patients, 9 patients will not fit primary analysis thus, would increase total enrollment to 90 patients in order to reach 40 that would fit primary analysis. We will enroll 90 patients over both sites.

10.4 * PARTICIPANT AGE RANGE: Eligible age ranges: (REQUIRED)

- ☐ 0-6 years
- ☐ 7-12 years
- ☐ 13-17 years
- ☒ 18-64 years
- ☒ 65+

10.5 * STUDY POPULATIONS: Data will be collected from or about the following types of people (check all that apply): (REQUIRED)

- ☒ Inpatients
- ☐ Outpatients
- ☐ Family members or caregivers
- ☐ Providers
- ☐ People who have a condition but who are not being seen as patients
- ☐ Healthy volunteers
- ☐ Students
- ☐ Staff of UCSF or affiliated institutions
- ☐ None of the above

10.6 * SPECIAL SUBJECT GROUPS: Check the populations that may be enrolled: (REQUIRED)

- ☐ Children / Minors
- ☒ Subjects unable to consent for themselves
- ☐ Subjects unable to consent for themselves (emergency setting)
- ☒ Subjects with diminished capacity to consent
- ☒ Subjects unable to read, speak or understand English
- ☐ Pregnant women
- ☐ Fetuses
- ☐ Neonates
- ☐ Prisoners
- ☐ Economically or educationally disadvantaged persons
- ☐ None of the above

If not already addressed in the Background and Significance questions in the Research Plan section or elsewhere, explain why it is appropriate to include the types of subjects checked above in this particular study:

It is appropriate to include patients who cannot consent for themselves or have diminished capacity to consent due to the nature of their critical illness (e.g. neurologically injured) or the therapies they are receiving (e.g. sedating medications) to achieve the aim of understanding the response and safety of the study intervention on body temperature. It is common for neuro-critically ill patients with fever to have a condition or therapy-induced situation that renders them unable to consent for themselves.

We do not want to exlcude non-English speaking patients or surrogates. We do not expect a high number of non-English speaking patients or surrogates.

Describe the additional safeguards that have been included in the study to protect the rights and welfare of these subjects and minimize coercion or undue influence:

Here are some examples:

- evaluating capacity to consent for individuals who may be decisionally impaired (specify how)
- calibrating payment amounts to be non-coercive for the financially disadvantaged
- conducting more in-depth evaluations of subjects’ understanding of the study and the voluntary nature of participation
- involving advocates in the consent process

More information and other safeguards are described here: [Vulnerable Subject Populations](#) and [Recruiting Staff and Students](#).

Additional safeguards that will be put in place to protect subjects who are unable to consent for themselves include the procedure for obtaining consent from a surrogate if the subject is unable to consent along with informing the subject about their participation in the study when they regain ability to participate in the consent process. They will be given the option to decline consent at that time.

10.7 INCLUSION CRITERIA: Briefly describe the population(s) that will be involved in this study. Include anyone that data will be collected from or about (e.g. patients, healthy controls, caregivers, providers, administrators, students, parents, family members, etc.):

1. age ≥ 18 years old
2. weight ≥ 40 kg
3. at least one reading of body temperature ≥ 38.3 °C
4. diagnosis of subarachnoid hemorrhage, intracerebral hemorrhage, traumatic brain injury, subdural hematoma, or ischemic stroke
5. admission to the Intensive Care Unit at UCSF Medical Center or Zuckerberg San Francisco General Hospital.

10.8 EXCLUSION CRITERIA: List any exclusion criteria (e.g. reasons why someone would not be included in the study):

1. bromocriptine or acetaminophen hypersensitivity or allergy
2. known contraindication to bromocriptine— known ergot alkaloid hypersensitivity, known history of syncopal migraine
3. contraindication to nasogastric tube or swallowing pills
4. contraindication to esophageal, rectal or urinary temperature probe
5. current diagnosis of acute liver failure, acute liver injury, or prior diagnosis of cirrhosis
 1. Acute presentation (< 26 weeks), evidence of coagulation abnormality: international normalized ratio (INR) ≥ 2 ; evidence of liver damage: alanine aminotransferase (ALT) of $10 \times$ normal value; and any degree of mental status alteration
5. currently being treated with intra or extravascular therapeutic hypothermia – or where therapeutic hypothermia treatment is anticipated during study period
6. hyperthermic syndromes: heat stroke, evidence of thyrotoxicosis, malignant hyperthermia, neuroleptic malignant syndrome, or other drug-induced hyperthermia
7. administration of acetaminophen or acetaminophen containing medications within 9 hours prior to fever presentation
8. administration of non-steroidal anti-inflammatory drugs (NSAIDs) within 6 hours prior to fever presentation or aspirin > 300 mg less than 1 hour prior to fever presentation.
9. pregnancy or women in the post-partum period (6 months after delivery)
10. extracorporeal blood circuit therapies: replacement therapy, extracorporeal life support (ventricular assist device, extracorporeal membrane oxygenation) during study period
11. anticipated ICU stay < 48 hours
12. creatinine clearance ≤ 30 mL/min
13. severe cardiovascular disease (especially unstable angina or severe valvular disease)
14. patients already taking bromocriptine for other indications

10.9 * RESEARCH CONDUCTED ON PATIENT CARE WARDS: Do any study activities take place on patient care units at UCSF medical facilities: (REQUIRED)

☒ Yes ☐ No

Attach a letter of acknowledgement for the study from the involved patient care manager. If you don't know who the patient care manager is, click [here](#) to send an email to the nursing group.

11.0 Recruitment and Consent

11.1 * RECRUITMENT METHODS: What kinds of methods will be used to identify potential participants for recruitment (check all that apply): (REQUIRED)

- ☒ Medical records review
- ☐ Recruitment registry
- ☐ Re-contact of participants from the investigators' previous studies
- ☐ Referrals from colleagues (attach the 'Dear Colleague' letter or other recruitment materials you will provide to colleagues)
- ☐ Referrals from the community / word of mouth
- ☐ Advertisements (flyers, brochures, radio or t.v. ads, posting on clinical research sites or social media, presentation of the study at community events/media, etc.)
- ☐ Online recruiting tool such as TrialSpark
- ☐ CTSI Recruitment Services unit
- ☐ Other method (describe below)

11.2 * SEARCHING OF MEDICAL RECORDS: (REQUIRED)

Whose patients are they:

- ☒ Investigators' own patients or patients seen within the same practice
- ☒ Patients not under the care of the investigators

How and by whom will records be accessed and searched (check all that apply):

- ☒ Self-search in APeX or other medical records source
- ☐ Self-search using UCSF's Research Cohort Selection Tool
- ☐ CTSI Consultation Service Recruitment Services
- ☐ UCSF Academic Research Services (ARS)
- ☐ University of California Research Exchange (UC ReX)
- ☐ Other method (describe below)

11.3 DETERMINATION OF ELIGIBILITY: How, when, and by whom will eligibility for recruitment be determined:

When patients are admitted to the neuro ICU, a member of the research team will perform initial screening for eligibility through the EMR, discuss with the primary team and consent the patient or surrogate if the patient meets inclusion and exclusion criteria. The research team may be contacted by nurses, primary team members or ICU team members. The research team will be doing all screening and recruitment.

11.4 * INITIATION OF CONTACT: Who initiates contact (check all that apply): (REQUIRED)

- ☒ Investigators/study team

- ☐ UCSF recruitment unit (e.g. CTSI Consultation Services)
- ☐ Potential participant
- ☐ Other (explain below)

11.5 * HOW IS CONTACT INITIATED: (check all that apply): (REQUIRED)

- ☒ In person
- ☐ Phone
- ☐ Letter / email
- ☐ Website or app
- ☐ Other (explain below)

11.6 RECRUITMENT PLAN: Based on the checkboxes you chose above, please provide a narrative describing your recruitment plan. We want to know:

- **Who is conducting the search for potential participants, and how?**
- **How are potential subjects being approached for recruitment? By whom, and when?**

If there will be more than one participant group (e.g. patients, healthy controls, caregivers, family members, providers, etc.), provide details about the recruitment plans for each group. (Recommended length - 100-250 words)

When a patient is admitted to the neuro ICU, the research team will be contacted by the ICU charge nurse, ICU nurse, ICU team, or primary team or the research team member may find that a new patient has been admitted through APEX. If the patient is eligible, a member of the research team will discuss the appropriateness of the patient with the primary team. After determining appropriateness with the team and eligibility criteria are met, the research team member will approach the patient in the ICU room for the informed consent process. Potential subjects will be given as much time as they need to consider whether to enroll in the study. In the situation when a patient clearly agrees to participate in the study, but is unable to sign the consent form because of a physical impairment, such as the temporary inability to use a writing instrument due to limited mobility, device interference (e.g. arterial line, arm board), localized edema, and or extremity injury, a present family member or ICU nurse can provide witnessed consent for the patient's signature. All procedures will be done in a manner that protects the human subject from research risks.

If it is determined that the patient is unable to participate in the consent process, the research team member will describe the research protocol to the patient and indicate the intent to obtain surrogate consent. If there are no indications of resistance or dissent, the research team member will approach the patient's surrogate in the ICU and go to a private location proximal to the ICU room for the informed consent process. Patient surrogates will be given as much time as they need to consider consent for participation in the study.

If for any reason, the patient or surrogate decides they initially do not want to participate in the study but then later would like to participate after the patient becomes febrile, the research team will re-screen the patient to make sure the patient is still eligible. If the patient is eligible, they can be enrolled in the study at that time. Timing of medical intervention will be based off of 1) the washout period of any antipyretics given prior to enrollment and 2) timing of last body temperature of the patient ≥ 38.3 °C (must be within 1 hour of study medication administration).

11.7 * CONSENT METHODS: How will permission to participate (i.e., informed consent) be obtained from each potential participant. If there will be multiple groups and different plans for consenting each, check all that apply. See the orange Help bubble to the right for more detailed guidance. Participants will (check all that apply): (REQUIRED)

- ☒ Sign a consent form at the end of the consent discussion (signed consent)
- ☐ Provide online 'eConsent' using DocuSign or another E-Signature system
- ☐ Click through a link in a survey or email after reading about the study and then complete the study online (electronic consent)
- ☐ Be told about the study and be given a handout/information sheet and be asked if they agree to participate (verbal consent)
- ☐ Complete the study activities and turn in materials, as in the case of a completed survey that is placed in a drop box or mailed to the study team (implied consent)
- ☒ Not be able to provide consent and will have a family member consent for them, as in the case of a critically ill or unconscious patient (surrogate consent)
- ☐ Not be able to provide consent (emergency waiver of consent - allowed for minimal risk research or greater than minimal risk research with an approved community consultation plan)
- ☐ Not know about the study, as in the case of chart reviews or observations of public behavior (waiver of consent)
- ☐ Other method (describe below)

Attach your consent form, information sheet, or electronic consent text in the Informed Consent Documents section of the Initial Review Submission Packet Form.

- 11.8 * **CONSENT PROCESS: Describe the process for obtaining informed consent, including details such as who will have the consent discussion and when participants will be asked to sign the consent form in relation to finding out about the study: (REQUIRED)** We encourage researchers to review our [guidance on obtaining and documenting informed consent](#).
- **If there are multiple groups being consented differently, provide details about the consent process for each group.**
 - **If you are relying on verbal or implied consent, provide details about how that will happen.**
 - **For studies using online recruitment and consent or consent via mail, provide details here.**

After the research team member identifies an eligible patient and the patient’s primary service physician determines approval for participation in the study, the eligible patient’s nurse will be approached and asked if the patient is able to participate in the informed consent process as evidenced by being alert, able to answer questions and follow commands. The patient will be approached by the research team member who will complete the informed consent process if the nurse reports the patient is able to participate appropriately. If the nurse reports that the patient is not able to participate appropriately, the patient’s surrogate (legally authorized representative) will be identified and contacted to obtain informed consent.

Patients or surrogates will be informed about the purpose of the study and its potential benefits to future ICU patients by providing direction for clinical practice of fever management and for future studies on the management of fever in critically ill patients. They will be informed that there is no direct benefit from participating in the study. However, information that patients provide may help critical care professionals learn how to improve patient care related to fever management with bromocriptine. Informed consent will be documented by the patient’s or surrogate’s signature on the approved consent form. In situations when a patient clearly agrees to participate in the study, but is unable to sign the consent form because of physical impairment, such as the temporary inability to

hold a pen due to localized swelling, extremity injury or limited mobility, the patient’s family member or ICU nurse may sign the consent as a witness. The patient or surrogate will be informed that they do not have to participate and that they can refuse continued participation in the study at any time. They will be told that their decision to not participate or stop participation in this study will have no influence on the patient’s treatment in ICU. We will ask the patient or surrogate if they have any questions about the study or about any of its procedures and provide further clarification if necessary. The patient or surrogate will be asked to answer two questions to evaluate their understanding of information provided: 1) Do you understand that you will receive 48 hours of a standard of care medication - acetaminophen or a standard of care medication - acetaminophen and the new intervention medication - bromocriptine in this study? (answer: yes) and 2) Who do you let know if you do not want to continue in the study? (answer: ICU nurse or research team member).

*** It is important that the people obtaining consent are qualified to do so. Briefly describe the training and experience these individuals have in obtaining informed consent: (REQUIRED)**

Judy Ch'ang, MD - current neurocritical care fellow; has obtained informed consent for various procedures and clinical trials throughout her training as a resident-physician and continued as a fellow.

Michael Trillanes, PharmD, BCPS, BCCCP - Neurocritical care pharmacist at UCSF Parnassus. Has witnessed informed consent being obtained for studies and procedures and will be trained on how to obtain informed consent.

Kristin Slown, PharmD, BCPS - Critical care pharmacist at ZSFGH. Has witnessed informed consent being obtained for studies and procedures and will be trained on how to obtain informed consent.

Melissa Nguyen, PharmD, BCPS - Critical care pharmacist at ZSFGH. Has witnessed informed consent being obtained for studies and procedures and will be trained on how to obtain informed consent.

Jeff Vitt, MD - current neurocritical care fellow; has obtained informed consent for various procedures throughout training as a resident-physician and continued as a fellow.

Chung Huan Sun, MD - current neurocritical care fellow; has obtained informed consent for various procedures and clinical trials throughout training as a resident-physician and continued as a fellow.

Ivy Nguyen, MD - current neurovascular fellow; has obtained informed consent for various procedures throughout training as a resident-physician and continued as a fellow.

Arturo Montano, MD - current neurocritical care fellow; has obtained informed consent for various procedures throughout training as a resident-physician and continued as a fellow.

11.9 * CONSENT COMPREHENSION: Indicate how the study team will assess and enhance the subjects' understanding of study procedures, risks, and benefits prior to signing the consent form (check all that apply): (REQUIRED) Tip: Review the Consent Comprehension - Learning Notes in the Help bubble at the right for specific questions that can be asked to assess comprehension, consider using the UCSF Decision-Making Capacity Assesment Tool, and review our guidance on obtaining written or verbal informed consent for more detail on how to conduct the assessment.

☒ The study team will engage the potential participant in a dialogue, using open-ended questions about the nature of the study or the experimental treatment, the risks and benefits of participating, and the voluntary nature of participation

- ☒ Potential participants will be asked or shown a series of questions to assess their understanding of the study purpose, procedures, risks and benefits, as well as the voluntary nature of participation (especially appropriate when the consent process happens online or through a mobile health app)
- ☐ Other method (describe below):

Provide details of the other approaches that will be used, if using another method to assess comprehension:

The patient or surrogate will be asked to answer two questions to evaluate their understanding of information provided: 1) Do you understand that you will receive 48 hours of a standard of care medication - acetaminophen or a standard of care medication - acetaminophen and the new intervention medication - bromocriptine in this study? (answer: yes) and 2) Who do you let know if you do not want to continue in the study? (answer: ICU nurse or research team member).

11.11 * NON-ENGLISH CONSENT METHOD: Indicate which method(s) you will use to consent non-English speaking subjects: (REQUIRED)

- ☐ Preferred Method—Consent form and other study documents will be available in the subject's primary language Personnel able to discuss participation in the patient's language will be present for the consent process.
- ☒ Short-Form—A qualified interpreter will translate the consent form verbally, and subjects will be given the Experimental Subject's Bill of Rights in their primary language, following instructions in Those Who do not Read, Speak or Understand English for required witnessing and signatures

*** Explain how you will maintain the ability to communicate with non-English speakers throughout their participation in the study: (REQUIRED)**

We will rely on hospital translators to communicate with the patient as we do in standard practice. For patients wishing to speak with the study team or PI, office phone numbers will be provided along with written explanation of how to obtain interpreter for phone calls.

11.13 TIME: What is the estimated time commitment for participants (per visit and in total):

Time duration for study protocol is approximately 48 hours per patient. 60 patients x 48 hours = 2880 hours.

30 Day phone call follow-ups will be approximately 15 minutes

IMPORTANT TIP: Ensure this information is consistent with the information provided in the consent form.

11.14 ALTERNATIVES: Is there a standard of care (SOC) or usual care that would be offered to prospective participants at UCSF (or the study site) if they did not participate in this research study:

☒ Yes ☐ No

Describe the care that patients would ordinarily receive at the medical center if they did not participate in this study (provide details, assuming that some of the IRB members are not specialists in this field):

Throughout the different teams on neurology and neurosurgery, the treatment of fever is different. Patients who would not participate in this study would likely receive acetaminophen at various doses and dosing intervals and variable use of a cooling blanket versus ice packs. NSAIDs such as ibuprofen are rarely used in neurosurgery or neurovascular cases given its potential risk of increasing bleeding. If fevers are correlated with increased intracranial pressures and traumatic brain injury, very rarely, cooling catheters are placed at ZSFGH.

11.15 OFF-STUDY TREATMENT: Is the study drug or treatment available off-study:

- ☒ Yes
☐ No
☐ Not applicable

12.0 Waiver of Consent/Authorization for Recruitment Purposes

This section is required when medical records may be reviewed to determine eligibility for recruitment.

12.1 * PRACTICABILITY OF OBTAINING CONSENT PRIOR TO ACCESS: Study personnel need to access protected health information (PHI) during the recruitment process and it is not practicable to obtain informed consent until potential subjects have been identified: (REQUIRED)

☒ Yes

If **no**, a waiver of consent/authorization is NOT needed.

12.2 * RISK TO PRIVACY: A waiver for screening of health records to identify potential subjects poses no more than minimal risk to privacy for participants:

☒ Yes

If **no**, a waiver of authorization can NOT be granted.

12.3 * RIGHTS/WELFARE: Screening health records prior to obtaining consent will not adversely affect subjects' rights and welfare:

☒ Yes

If **no**, a waiver of authorization can NOT be granted.

12.4 * IDENTIFIERS: Check all the identifiers that will be collected prior to obtaining informed consent:

- ☒ Names
☒ Dates

- ☐ Postal addresses
- ☐ Phone numbers
- ☐ Fax numbers
- ☐ Email addresses
- ☐ Social Security Numbers*
- ☒ Medical record numbers
- ☐ Health plan numbers
- ☐ Account numbers
- ☐ License or certificate numbers
- ☐ Vehicle ID numbers
- ☐ Device identifiers or serial numbers
- ☐ Web URLs
- ☐ IP address numbers
- ☐ Biometric identifiers
- ☐ Facial photos or other identifiable images
- ☐ Any other unique identifier
- ☐ None

Note: HIPAA rules require that you collect the minimum necessary.

12.5 * HEALTH INFORMATION: Describe any health information that will be collected prior to obtaining informed consent:

Patient information that will be collected prior to obtaining consent include the inclusion and exclusion criteria from the medical record which includes: patient diagnoses, age, weight, laboratory results, vital signs, antipyretic medications ordered and recorded, allergies, if they are taking pills by mouth or per nasogastric tube, pregnancy status (if appropriate), presence of extracorporeal blood circuit therapies and if anticipated ICU stay is < 48 hours.

Note: HIPAA requires that you collect the minimum necessary.

12.6 * DATA RETENTION/DESTRUCTION PLAN: Describe your plan to destroy any identifiable data collected to determine eligibility for recruitment. This should be done at the earliest opportunity. If you plan to retain identifiable recruitment data, provide the justification for doing so:

Data will be coded and the data key will be destroyed at the end of the study or by November 31, 2019.

13.0 Surrogate Consent

13.1 PSYCHIATRIC SCREEN: Are any subjects inpatients on a psychiatric ward or mental health facility, or on psychiatric hold:

☒ No

If Yes, use of surrogate consent for research is NOT allowed in California.

13.2 AREAS OF RESEARCH: Is this study related to the cognitive impairment, lack of capacity, or serious or life-threatening diseases and conditions of the research subjects:

☒ Yes

13.3 JUSTIFICATION: Explain why use of surrogates is necessary for completion of this study:

It is important to use surrogates to consent for this study as it can be common for critically ill patients with fever to have a condition or therapy-induced situation that renders them unable to consent for themselves. It is appropriate to include patients who cannot consent for themselves due to the nature of their critical illness (e.g. neurologically injured) or the therapies they are receiving (e.g. sedating medications) to achieve the aim of understanding the response of the study intervention on body temperature and its safety.

13.4 COGNITIVE ASSESSMENT: Describe the plans for assessing the decision-making capacity of prospective subjects:

After the research team member identifies an eligible patient and the patient's primary service physician determines approval for participation in the study, the eligible patient's nurse will be approached and asked if the patient is able to participate in the informed consent process as evidenced by being alert, able to answer questions and follow commands. If the patient is unable to participate in the consent process, the patient's legally authorized decision-maker (surrogate) will be contacted and informed about the purpose of the study and its potential benefits to future ICU patients by providing direction for clinical practice of fever management and for future studies on the management of fever in critically ill patients. The surrogate will be informed that there is no direct benefit from participating in the study. However, information that patients provide may help critical care professionals learn how to improve patient care related to fever management with the addition of bromocriptine. Informed consent will be documented by the surrogate's signature on the approved consent form and the Self-Certification of Surrogate Decision Makers for Potential Subject's Participation in University of California Research form will be filled out and signed by the surrogate and a witness as evidence of the willingness of the person to serve as a surrogate. When the surrogate is not present in the hospital, the research team member will contact the surrogate via telephone for the informed consent process if they are in agreement and have access to a facsimile device to receive and transmit the consent form and the Self-Certification of Surrogate Decision Makers for Potential Subject's Participation in University of California Research form.

13.5 POST-ENROLLMENT CONSENT PLANS: Describe the plans for obtaining consent from subjects who regain ability to consent after a surrogate has given initial consent:

The informed consent process will be applied to patients who regain their capacity for decision making during their ICU stay.

13.6 SURROGATE CONSENT REQUIREMENTS: Check to acknowledge:

- ☒ Research takes place in California. All surrogates will complete the "Self-Certification of Surrogate Decision Makers for Participation in Research" form.
- ☒ Conscious subjects will be notified of the decision to contact a surrogate. If subjects object to study participation, they will be excluded even if their surrogate has given consent.
- ☒ Surrogates will not receive any financial compensation for providing consent.
- ☒ If a higher-ranking surrogate is identified at any time, the investigators will defer to the higher-ranking surrogate's decision regarding the subject's participation in the research.

For research taking place outside of California, explain how investigators will confirm that surrogates are legally authorized representatives:

14.0 Risks and Benefits

14.1 RESEARCH-RELATED RISKS: Check if your study involves any of these specific research-related risks to participants that may need to be disclosed in the consent form:

- ☒ For interventional studies, risk that the regimen may be more harmful or less effective than other available interventions
- ☐ Risks associated with radiation exposure for imaging studies specifically for research purposes
- ☐ Risks associated with the administration of contrast agent for imaging studies
- ☐ Risks associated with withholding of treatment or discontinuation of current treatment (e.g., washout period is required by the study protocol)
- ☐ For randomized, placebo-controlled trials, possible temporary or permanent health consequences from the deprivation of effective therapies during the placebo administration period
- ☐ For studies involving a sham surgical procedure, the risk that participants may experience increased morbidity without the possibility of benefit
- ☐ Risks associated with modification or extension of a surgical procedure primarily for research purposes (e.g. risks associated with prolonging anesthesia, time in the operating room, etc.)
- ☐ Risk of pain or physical discomfort caused by the research intervention
- ☐ Possible personal discomfort due to sensitive topics (stress, embarrassment, trauma)

* For any boxes checked above, describe how you will minimize these risks and discomforts, e.g., adding or increasing the frequency of monitoring, additional screening to identify and exclude people with diminished kidney or liver function, or modification of procedures such as changing imaging studies to avoid giving contrast agent to people who are more likely to suffer side effects from it, etc.: **(REQUIRED)**

There are side effects associated with bromocriptine. There is already extensive clinical trial data from its various other indications and case reports in the literature documenting its side effects and safety parameters. Already, through the exclusion criteria, patients that are not good candidates for either medication, acetaminophen and bromocriptine, will not be included in the study such as a past medical history of cirrhosis or a current diagnosis of acute liver failure or diminished kidney function. From the package insert, bromocriptine has different side effects in patients with different indications (hyperprolactinemia, acromegaly, Parkinson's disease). In pregnant patients, it is category B, thus pregnant women and lactating women will be excluded from the study.

Per the package insert for hyperprolactinemia, "Therapy was discontinued in approximately 5% of patients because of adverse effects... nausea (49%), headache (19%), dizziness (17%), fatigue (7%), lightheadedness (5%), vomiting (5%), abdominal cramps (4%), nasal congestion (3%), constipation (3%), diarrhea (3%) and drowsiness (3%)."

Per the package insert for acromegaly, "nausea (18%), constipation (14%), postural/orthostatic hypotension (6%), anorexia (4%), dry mouth/nasal stuffiness (4%), indigestion/dyspepsia (4%), digital vasospasm (3%), drowsiness/tiredness (3%) and vomiting (2%). Less frequent adverse reactions (less than 2%) were: gastrointestinal bleeding, dizziness, exacerbation of Raynaud's syndrome, headache and syncope. Rarely (less than 1%) hair loss, alcohol potentiation, faintness, lightheadedness, arrhythmia, ventricular tachycardia, decreased sleep requirement, visual hallucinations, lassitude, shortness of breath, bradycardia, vertigo, paresthesia, sluggishness, vasovagal attack, delusional psychosis, paranoia, insomnia, heavy headedness, reduced tolerance to cold, tingling of ears, facial pallor and muscle cramps have been reported."

Per the package insert for Parkinson's disease, "In clinical trials in which Parlodel was administered with concomitant reduction in the dose of levodopa/carbidopa, the most common newly appearing adverse reactions were: nausea, abnormal involuntary movements, hallucinations, confusion, "on-off" phenomenon, dizziness, drowsiness, faintness/fainting, vomiting, asthenia, abdominal discomfort, visual disturbance, ataxia, insomnia, depression, hypotension, shortness of breath, constipation, and vertigo."

The effect of liver or renal impairment on the pharmacokinetics of bromocriptine and its metabolites is not known and has not been specifically evaluated. As only 6% is eliminated via the kidney, renal impairment may not have significant impact on the pharmacokinetics of bromocriptine and its metabolites. Since Parlodel is mainly eliminated by hepatic metabolism, liver impairment may increase the plasma levels of bromocriptine, therefore, any patient with cirrhosis or a new diagnosis of liver failure or liver injury will be excluded in this study.

The side effects of acetaminophen are skin rash, pancytopenia, hypersensitivity reaction, and hepatic injury including liver failure. Thus, any patient with cirrhosis or a new diagnosis of liver failure or liver injury will be excluded in this study. It is recommended that in cases of severe renal impairment (creatinine clearance \leq 30 mL/min), longer dosing intervals and a reduced total daily dose is warranted. Patients with a creatinine clearance \leq 30 mL/min will also be excluded from the study.

In order to capture side effects, bed side nurses will do 4 assessments (once every shift) of the patient specifically looking at common side effects of bromocriptine. Also, the patients will be monitored closely in the ICU setting for any other vital sign changes.

If patients have an esophageal, bladder, or rectal temperature probe for any other indication, they will continue to have these probes.

14.2 RISKS: Describe any anticipated risks and discomforts not listed above:

Patients must have routine bladder, esophageal, or rectal temperature probes. Because of the difference in temperature data gathering and the different sensitivities between oral versus bladder, esophageal, and rectal probes, we are not allowing oral temperature data gathering. These invasive probes may cause discomfort and carry their own risks, but they are also part of routine care in this patient population. If the patient refuses placement of any of these invasive probes, then they cannot be in the study.

- 14.3 MINIMIZING RISKS: Describe the steps you have taken to minimize the risks/discomforts to subjects. Examples include:
- designing the study to make use of procedures involving less risk when appropriate
 - minimizing study procedures by taking advantage of clinical procedures conducted on the study participants
 - mitigating risks by planning special monitoring or conducting supportive interventions for the study
 - having a plan for evaluation and possible referral of subjects who report suicidal ideation

The nursing assessments are designed to be very simple and time efficient for nursing to do which will not be invasive to patients. Also, patients will be told that they do not have to participate and they can refuse continued participation in the study at any point during the study period.

14.4 RESOURCES: Describe the resources in place to conduct this study in a way that assures protection of the rights and welfare of participants: These resources typically include appropriately trained and qualified personnel (in terms availability, number, expertise and experience), funding, space, equipment, and time to devote to study activities. Depending on the nature of the research study, investigators should consider the proximity or availability of critical resources that may be essential to the safety and welfare of participants, such as

- the proximity of an emergency facility for care of participant injury
- availability of psychological support after participation
- resources for participant communication, such as language translation services

This study protocol will be funded by departmental funds. The research team members are well versed in HIPAA and informed consent. The data analysts in Dr. Xiao Hu's lab, who will be blinded to treatment group, are experienced in doing this type of data analysis from ICU 8 and 11 in a private and confidential manner. If patients have any side effects, they will already be in the ICU and diagnostic studies and treatments can be initiated immediately.

14.5 * BENEFITS: (REQUIRED) Note: These are the benefits that the IRB will consider during their review. They are not necessarily appropriate to include in the consent form.

Possible immediate and/or direct benefits to participants and society at large (check all that apply):

- ☐ Positive health outcome (e.g. improvement of condition, relief of pain, increased mobility, etc.)
- ☐ Closer follow-up than standard care may lead to improved outcomes or patient engagement
- ☐ Health and lifestyle changes may occur as a result of participation
- ☒ Knowledge may be gained about their health and health conditions
- ☒ Feeling of contribution to knowledge in the health or social sciences field
- ☐ The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children
- ☐ Other benefit (describe below)
- ☐ None

14.6 RISK TO BENEFIT RATIO: Explain why the risks to subjects are reasonable in relation to anticipated benefits, if any, to the participant or society:

There is no direct benefit to the patient from participating in this study. However, the information that patients provide may help guide health professionals in improving care of future neurocritical care patients with fever and may change the overall management of these patients across the country. The clinical decision-making for implementing fever management interventions and body temperature thresholds for administration of antipyretic agents is variable in current practice and medical therapy for fever control is overall ineffective. Currently, giving patients acetaminophen is the standard of care and then use of external and intravascular cooling is variable. The risks of bromocriptine with our current knowledge of the medication's side effects appear to be low. When used in the aforementioned case reports, prospective TBI study, and retrospective SAH abstract where all patients

were neurocritically ill patients, no side effects were noted. This study will help us identify in a prospective manner the safety profile in this critically ill population. Future benefits to neurocritically ill patients include the potential development of evidence- based recommendations for use of bromocriptine to treat fever during critical illness based on this study's findings. Future benefits also include the potential to identify the etiology of fever (central versus infectious) based off of the difference of fever response to bromocriptine which could possibly be addressed in future studies. Future benefits also include decreased used of external and intravascular cooling devices which also means decreased need for anti-shivering medications and sedation. There is potential for the study findings to guide use of acetaminophen and bromocriptine in neurocritically ill patients which has potential impact on health care resource utilization.

15.0

Data and Safety Monitoring Plan

15.2

* DATA AND SAFETY MONITORING PLAN: (REQUIRED)

All greater than minimal risk studies are required to provide a plan. Lack of an adequate plan is one of the most common reasons why IRB approval is delayed.

Instructions:

Describe the plan for monitoring data quality and participant safety. Key areas that should be included in the plan are:

- An explanation of the plan to monitor data collection, study progress, and safety
- A description of who will perform the monitoring and at what frequency (e.g., the PI only, a contract research organization, a Data and Safety Monitoring Board or Data Monitoring Committee, etc.)
- The type of data and events that will be reviewed (e.g., adverse events, breaches of confidentiality, unanticipated problems involving risk to participants or others, unblinded efficacy data, etc.)
- Procedures and timeline for communicating monitoring results to the UCSF IRB, the study sponsor, and other appropriate entities
- Assurance that the research team will adhere to the UCSF IRB reporting requirements

As appropriate:

- A plan for conducting and reporting interim analysis
- Clearly defined stopping rules
- Clearly defined rules for withdrawing participants from study interventions

The Principal Investigator (PI), Dr. Judy Ch'ang, has primary responsibility for the overall conduct of the study and for the safety of the participating human subjects. The PI will ensure that 1) the informed consent process is conducted appropriately and that informed consent is obtained prior to proceeding with any study procedures; 2) only eligible subjects, per protocol eligibility criteria, are enrolled in the study; 3) data are collected per protocol requirements; 4) the control and intervention drug administration protocol is followed properly and consistently; 5) procedures are implemented to ensure that the project is consistently monitored for possible adverse events; 6) the privacy and

confidentiality of the study subjects is maintained; and, 7) patients are aware of their rights as research subjects and who/how to reach nurses and research team members regarding stopping the study. Each patient will be provided with a copy of the Experimental Subject’s Bill of Rights. In the event that a patient would like to withdraw from the study, their temperature and antipyretic data can be used for research until that point, but from when they chose to leave the study, their temperature and other vitals data will not be recorded or monitored.

If adverse events should occur, they will be reviewed promptly and reported as required to the UCSF Committee on Human Research. The PI will conduct interim analyses of study information and data to assure the continuing safety of research participants, efficacy of the study intervention, and the appropriateness of the study. While implementation of aspects of the Data and Safety Monitoring plan may be delegated to members of the research team, the PI maintains ultimate responsibility for the project and for safety of study participants. After enrolling 30 patients, the PI will conduct and report an interim analysis. There will not be an independent Data Safety Monitoring Board Committee for this study.

15.3 * DATA AND SAFETY MONITORING BOARD (DSMB): Will a Data and Safety Monitoring Board (DSMB) be established: (REQUIRED)

- ☐ Yes
- ☒ No

Guidelines

A Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) is a formal, independent committee that is specifically established to conduct interim monitoring, oversight and analysis of study information and data to assure the continuing safety, efficacy, appropriateness, relevance, and integrity of the study.

The UCSF IRB reserves the right to request a DSMB/DMC for any study. However, the following are factors that the IRB will consider when making this determination:

- There is a significant likelihood of a serious adverse event to subjects
- The study is conducted at multiple sites and the level of risk is greater than minimal
- The study generates data that are blinded or randomized
- The study involves a large number of patients randomized to one of two or more interventions
- A study for which the performance of an interim analysis is crucial for the protection of the subjects
- First use in humans
- First use in children
- The study involves gene transfer, stem cell therapy, or other novel interventions for which long-term outcome data are not known or available

16.0 Confidentiality, Privacy, and Data Security

16.1 PROTECTING PRIVACY: Indicate how subject privacy will be protected:

- ☒ Conduct conversations about the research in a private room
- ☒ Ask the subject how they wish to be communicated with – what phone numbers can be called, can messages be left, can they receive mail about the study at home, etc.
- ☒ Take special measures to ensure that data collected about sensitive issues do not get added to their medical records or shared with others without the subject's permission
- ☐ Other methods (describe below)

16.2 SENSITIVE DATA: Do any of the instruments ask about illegal or stigmatized behavior:

☐ Yes ☒ No

16.3 CONSEQUENCES OF A LOSS OF PRIVACY OR CONFIDENTIALITY: Could a breach of privacy or confidentiality result in any significant consequences to participants, such as criminal or civil liability, loss of state or federal benefits, or be damaging to the participant's financial standing, employability, or reputation:

☒ Yes ☐ No

Describe the potential consequences:

Potential consequences related to loss of privacy related to hospitalization may lead to adverse social and/or employment consequences.

- ☐ Embarrassment
- ☐ Criminal or civil liability
- ☐ Loss of state or federal benefits
- ☒ Damaging to the participant's financial standing, employability, or reputation
- ☐ Potential risks to insurability (health, disability, or life insurance)

16.4 EXTRA CONFIDENTIALITY MEASURES: Explain any extra steps that will be taken to assure confidentiality and protect identifiable information from improper use and disclosure, if any:

The PI, co-investigators, and research team members have been certified in HIPAA regulations and data collection procedures and management are in compliance with HIPAA regulations. Electronically stored data will be de-identified. All identifying information will be kept separately from the data and secured electronically. We do not plan to share any personal identifying information outside the research team. We plan to only collect minimal patient identifying data: names, dates, and medical record numbers. The research team will access only the information pertaining to the inclusion and exclusion criteria before obtaining consent for the study from the patient or surrogate. Data will be kept in a locked office. Data will be coded and the data key will be destroyed at the end of study.

16.5 * REPORTABILITY: Do you anticipate that this study may collect information that State or Federal law requires to be reported to other officials, such as elder abuse, child abuse, or threat to self or others: (REQUIRED)

<input type="radio"/> Yes <input checked="" type="radio"/> No	
16.6 CERTIFICATE OF CONFIDENTIALITY: Will this study obtain a Certificate of Confidentiality:	
<input type="radio"/> Yes <input checked="" type="radio"/> No	
16.7 SHARING OF RESEARCH RESULTS: Will there be any sharing of EXPERIMENTAL research test results with subjects or their care providers:	
<input type="radio"/> Yes <input checked="" type="radio"/> No	
16.8 * IDENTIFIERS: Will any personal identifiers be collected: (REQUIRED)	
<div><input checked="" type="radio"/> Yes <input type="radio"/> No</div> <p>Check all the identifiers that may be included:</p> <div><input checked="" type="checkbox"/> Names <input checked="" type="checkbox"/> Dates <input type="checkbox"/> Postal addresses <input type="checkbox"/> Phone numbers <input type="checkbox"/> Fax numbers <input type="checkbox"/> Email addresses <input type="checkbox"/> Social Security Numbers* <input checked="" type="checkbox"/> Medical record numbers <input type="checkbox"/> Health plan numbers <input type="checkbox"/> Account numbers <input type="checkbox"/> License or certificate numbers <input type="checkbox"/> Vehicle ID numbers <input type="checkbox"/> Device identifiers or serial numbers <input type="checkbox"/> Web URLs <input type="checkbox"/> IP address numbers <input type="checkbox"/> Biometric identifiers <input type="checkbox"/> Facial photos or other identifiable images <input type="checkbox"/> Any other unique identifier</div> <p>* Could study records include ANY photos or images (even 'unidentifiable' ones): (REQUIRED)</p> <div><input type="radio"/> Yes <input checked="" type="radio"/> No</div>	
16.9 DATA DISCLOSURE: Will identifiable information be shared with outside groups:	
<input type="radio"/> Yes <input checked="" type="radio"/> No	

16.11 * DATA COLLECTION AND STORAGE: (check all that apply): (REQUIRED)

Collection methods:

- ☒ Paper-based (surveys, logs, diaries, etc.)
- ☐ Electronic case report forms (CRFs), such as OnCore or another clinical trial management portal
- ☐ Web-based online surveys or computer-assisted interview tool
- ☐ Mobile applications (mobile or tablet-based)
- ☐ Wearable devices
- ☐ Audio/video recordings
- ☐ Other:

*** Data will be collected/stored in systems owned by (check all that apply): (REQUIRED)**

- ☒ UCSF
- ☐ SF VAMC
- ☐ Amazon (Amazon Cloud)
- ☐ Other academic institution
- ☐ 3rd party vendor (business entity)
- ☐ Other (explain below)

16.12 DATA SECURITY: Indicate how data are kept secure and protected from improper use and disclosure (check all that apply): NOTE: Whenever possible, do not store subject identifiers on laptops, PDAs, or other portable devices. If you collect subject identifiers on portable devices, you MUST encrypt the devices.

- ☐ Data are stored securely in My Research
- ☒ Data are coded; data key is destroyed at end of study
- ☒ Data are coded; data key is kept separately and securely
- ☒ Data are kept in a locked file cabinet
- ☒ Data are kept in a locked office or suite
- ☒ Electronic data are protected with a password
- ☒ Data are stored on a secure network
- ☒ Data are collected/stored using REDCap or REDCap Survey
- ☐ Data are securely stored in OnCore

16.13 * DATA SECURITY: Confirm below that you will keep data confidential: (REQUIRED) I will keep any data sets that include identifiers secure and protected from improper use and disclosure by using methods such as:

- **Physical Security** – Keeping data in locked file cabinets, locked offices, locked suites, and physically securing computers and servers.
- **Electronic Security** – Following **UCSF minimum security standards for electronic information resources**, which includes (but is not limited to): not storing identifiers on portable devices like laptops or flash drives if they are unencrypted, encrypting portable devices, and storing data in password-protected files and on secure networks.

<div><input checked="" type="radio"/> Yes</div>	
<div>16.15 HIPAA APPLICABILITY: Study data will be:</div>	
<div><div><div><input type="checkbox"/> Derived from the Integrated Data Repository (IDR) or The Health Record Data Service (THREDS) at SFGH</div><div><input checked="" type="checkbox"/> Derived from a medical record (e.g. APeX, OnCore, etc. Identify source below)</div><div><input type="checkbox"/> Added to the hospital or clinical medical record</div><div><input type="checkbox"/> Created or collected as part of health care</div><div><input checked="" type="checkbox"/> Obtained from the subject, including interviews, questionnaires</div><div><input type="checkbox"/> Obtained ONLY from a foreign country or countries</div><div><input type="checkbox"/> Obtained ONLY from records open to the public</div><div><input type="checkbox"/> Obtained from existing research records</div><div><input type="checkbox"/> None of the above</div></div><div><p>Unless a waiver of Authorization is granted, in addition to the consent form, participants will need to sign UCSF Research Subject Authorization Form (HIPAA Form). NEW REQUIREMENT - This form should be uploaded in the Other Study Documents section of the Initial Review Submission Packet Form. Failure to obtain HIPAA Authorization for research is one of the most common findings from QIU Routine Site Visits. Your IRB approval letter will include instructions about HIPAA requirements specific to your study.</p><p>If derived from a medical record, identify source:</p><p>APEX (UCSF), ICCA (ZSFGH)</p></div></div>	
<div>16.16 * HIPAA - PERMISSION TO ACCESS SENSITIVE DATA: Does the research require access to any of the following types of health information from the medical record: (check all that apply) (REQUIRED)</div>	
<div><div><div><input type="checkbox"/> Drug or alcohol abuse, diagnosis or treatment</div><div><input type="checkbox"/> HIV/AIDS testing information</div><div><input type="checkbox"/> Genetic testing information</div><div><input type="checkbox"/> Mental health diagnosis or treatment</div><div><input checked="" type="checkbox"/> None of the above</div></div></div>	
<div>17.0 Financial Considerations</div>	
<div>17.1 * PAYMENT: Will subjects be paid for participation, reimbursed for time or expenses, or receive any other kind of compensation: (REQUIRED)</div>	
<div><div><div><input type="radio"/> Yes</div><div><input checked="" type="radio"/> No</div></div></div>	

17.4 COSTS TO SUBJECTS: Will subjects or their insurance be charged for any study activities:

☐ Yes ☒ No

18.0 Qualifications of Key Study Personnel

18.1 **NOTE: This information is required and your application will be considered incomplete without it.** If this study involves invasive or risky procedures, or procedures requiring special training or certification, please identify who will be conducting these procedures and provide details about their qualifications and training. Also identify each person who will be involved in the consent process. Click the orange question mark for more information and examples. Under qualifications, please include:

- Academic Title
- Institutional Affiliation (UCSF, SFGH, VAMC, etc.)
- Department
- Certifications

November, 2015 - NEW Definition of Key Study Personnel and CITI Training Requirements:

UCSF Key Study Personnel include the Principal Investigator, other investigators and research personnel who are directly involved in conducting research with study participants or who are directly involved in using study participants' identifiable private information during the course of the research. Key Personnel also include faculty mentors/advisors who provide direct oversight to Postdoctoral Fellows, Residents and Clinical Fellows serving as PI on the IRB application. The IRB requires that all Key Study Personnel complete Human Subjects Protection Training through CITI prior to approval of a new study, or a modification in which KSP are being added. More information on the CITI training requirement can be found on our website.

KSP Name	Description of Study Responsibilities - Briefly describe what will each person be doing on the study. If there are procedures requiring special expertise or certification, identify who will be carrying these out. Also identify who will be obtaining informed consent.	Qualifications, Licensure, and Training
Ch'ang, Judy	Co-principal investigator. Responsible for grant submission/revisions, study design, IRB submission/revision, subject enrollment, overall protocol conduct and safety of participating human subjects,	Physician and early in research career of critically ill patients. UCSF, Department of Neurology

	ongoing review of procedures and analysis of data.	
Kim, Anthony S	Co-principal investigator and mentor. Dr. Kim is responsible for study design, IRB submission/revision, grant submission and review. His role is to continue to review study procedures and participate in ongoing analysis and review of results.	Physician, medical director of the UCSF Stroke Center. He is a leader in the field of cerebrovascular diseases and an expert in statistics, serving as the head of Clinical and Translational Science Institute's Consultation Services including the Study Design Consultation Unit. He is an established researcher in care of neurovascular patients and has served as a principal investigator of numerous clinical trials at UCSF. UCSF, Department of Neurology
Schell-Chaple, Hildegard M	Co-investigator and mentor. Dr. Schell-Chaple is responsible for study design, IRB submission/revision, grant submission and review, and subject enrollment. Her role is to continue to review study procedures and participate in ongoing analysis and review of results.	PhD, clinical nurse specialist in adult critical care. Co-investigator and consultant to research studies in adult critical care units at UCSF over past 15 years. Has published her own study in the UCSF Medical Center ICUs on fever management. UCSF, Department of COO
Trillanes, Michael R	Study recruiter. He is responsible for helping with the study design pertaining to adverse effects and monitoring and patient enrollment. His role is to continue to participate in ongoing enrollment and reviewing results.	PharmD with a specialization in neurointensive care. UCSF, Department of Pharmacy
Villaroman, Andrea L	Study coordinator. She is responsible for patient enrollment helping obtain and analyze data. Her role is to participate in patient enrollment, ongoing analysis and review of results.	Study coordinator working for Dr. Hu's lab with ongoing experience related to IRB submission/revision, obtaining and analyzing results. UCSF, Department of Nursing
Slown, Kristin	Study recruiter. She is responsible for helping with the study design pertaining to adverse effects and monitoring and patient enrollment. Her role is to continue to participate in ongoing enrollment and	PharmD with a specialization in critical care. ZSFGH, Department of Pharmacy

	reviewing results.	
Nguyen, Melissa N	Study recruiter. She is responsible for helping with the study design pertaining to adverse effects and monitoring and patient enrollment. Her role is to continue to participate in ongoing enrollment and reviewing results.	PharmD with a specialization in critical care. ZSFGH, Department of Pharmacy
Randazzo, Dominica B	Her role is to continue to participate in ongoing enrollment and reviewing results.	Experienced CRC with CCRP certification
Dr. Singhal, Neel MD, PHD, MD PHD	Study recruiter. His role is to continue to participate in ongoing enrollment and reviewing results	MD, Neurocritical care attending at ZSFGH and UCSF
Chyall, Lawrence	Study recruiter. His role is to continue to participate in ongoing enrollment.	Nurse Practitioner, Neurosurgery SFGH
Mcguire, Daniel W	Study recruiter. His role is to continue to participate in ongoing enrollment.	Nurse Practitioner, Neurosurgery SFGH
Winkelman, Amy	Study recruiter. Her role is to continue to participate in ongoing enrollment.	Nurse Practitioner, Neurosurgery SFGH
Tran, Nhat	Biostatistician. Will blindly review results and data of these patients and do statistics.	PHD candidate, UCSF in Xiao Hu's lab (one of the investigators)
Vuong, Maximilian N	Coordinator. His role is to help with IRB issues.	Experienced Assistant CRC

19.0 Other Approvals and Registrations

19.1 * ADMINISTRATION OF RECOMBINANT DNA: Does this study involve administration of vaccines produced using recombinant DNA technologies to human subjects (Help Link added Aug '15): (REQUIRED)

☐ Yes ☒ No

19.2 * HUMAN GENE TRANSFER: Does this study involve human gene transfer (NOTE: Requires NIH Recombinant DNA Advisory Committee (RAC) review prior to IRB approval): (REQUIRED)

☐ Yes

☒ No

19.4 OTHER APPROVALS: Indicate if this study involves other regulated materials and requires approval and/or authorization from the following regulatory committees:

☐ Institutional Biological Safety Committee (IBC)

Specify BUA #:

☐ Institutional Animal Care and Use Committee (IACUC)

Specify IACUC #:

☐ Controlled Substances

20.0 End of Study Application

20.1 End of Study Application Form To continue working on the Study Application: Click on the section you need to edit in the left-hand menu. Remember to save through the entire Study Application after making changes. If you are done working on the Study Application: **Important:** Before proceeding, please go back to Section 4.0 Initial Screening Questions and Save and Continue through the form to make sure all the relevant sections and questions have been included. If you've changed any answers since you started, the branching may have changed. Your application will be incomplete and it will have to be returned for corrections. Once you are sure the form is complete, click Save and Continue. If this is a new study, you will automatically enter the Initial Review Submission Packet form, where you can attach consent forms or other study documents. Review the [Initial Review Submission Checklist](#) for a list of required attachments. Answer all questions and attach all required documents to speed up your approval.

The UCSF IRB wants your feedback about this new form. Please click the link to take a [brief survey](#) about the new application form.